

The Effects of Residential Greenness and Air Pollution on Oxidative Stress Levels in
Urban and Peri-urban Residents of Beijing

By

Wenhao Qi

Global Health Program
Duke Kunshan and Duke University

Date: _____

Approved:

Junfeng Zhang

John. S. Ji Advisor

Abu Abdullah

Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science in the
Global Health Program in the Graduate School
of Duke University and Duke Kunshan University

2021

The Effects of Residential Greenness and Air Pollution on Oxidative Stress Levels in
Urban and Peri-urban Residents of Beijing

by

Wenhao Qi

Global Health Program
Duke Kunshan and Duke University

Date: _____

Approved:

Junfeng Zhang Chair

John. S. Ji Advisor

Abu Abdullah Committee member

An abstract of a thesis submitted in partial
fulfillment of the requirements for the degree
of Master of Science in the
Global Health Program in the Graduate School of
Duke University and Duke Kunshan University

2021

Copyright by
Wenhao Qi
2021

Abstract

Background and Aims Exposure to air pollution has been associated with increased risks of cardiopulmonary diseases, cancer, and mortality. Simultaneously, greenspace has also been documented to be protective of mortality. Oxidative stress may be an intermediate biomarker in these processes. There has been little investigation on the effects of residential greenness and air pollution on oxidative stress. There are two aims of this study: 1) To explore the association of personal and ambient air pollution exposure with urinary oxidative stress levels; 2) To investigate the association of quantified-contemporary greenness with urinary oxidative stress levels and the interaction between greenness and air pollution exposure in affecting oxidative stress levels, respectively.

Methods In an existing panel study named AIRLESS (Effects of AIR pollution on cardiopulmonary disease in urban and peri-urban residents in Beijing), 123 residents living in an urban district (Haidian district) and 128 residents in a peri-urban district (Pinggu) of Beijing participated in the study. All participants were non-smokers, ≥ 49 years of age, and included 110 men and 140 women. Personal and ambient exposures to air pollutants were assessed for each participant during winter 2016 and summer 2017, respectively. Each participant was instructed to carry a validated personal air monitor (PAM) to measure particulate matters (PM_{10} , $PM_{2.5}$, and $PM_{1.0}$), nitrogen dioxide, carbon monoxide, and ozone concentrations at a high spatiotemporal resolution seven consecutive days in each sampling season. We calculated contemporaneous green space coverage level by the average daily satellite-derived Normalized Difference Vegetation Index (NDVI) in the zone with 500m*500m grids by Google Earth Engine (GEE) using the Moderate-resolution Imaging Spectroradiometer (MODIS) dataset from NASA

(National Aeronautics and Space Administration). We used the coordinates of the ambient air pollution monitoring stations and monitoring dates to match the NDVI data. Multiple oxidative stress biomarkers were measured, including urinary free malondialdehyde (MDA), urinary total MDA, and urinary 8-hydroxydeoxyguanosine (8-OHdG). All biomarkers were normalized by urinary creatinine in statistical analyses. Due to the right skewness, all biomarkers data were ln-transformed in the aim-specific analyses. (1) The association of personal and ambient air pollution exposure with the percent change of urinary oxidative stress biomarkers was estimated using linear mixed-effects models and the distributed lag linear model was used to investigate daily air pollutants' hysteresis effects on the percent change of urinary oxidative stress biomarkers. (2) The association between tertiary NDVI with urinary oxidative stress biomarkers was estimated using linear mixed-effects regression and subgroup analysis was used to test the robustness of the association between quantified NDVI with the mean percent change of oxidative stress biomarkers using the linear mixed-effects model in different groups. (3) To explore the interaction between greenness and air pollution in affecting oxidative stress by each of these exposure variables, stratified analyses were conducted to examine whether air pollution exposure modifies the effect of greenness and whether greenness modifies the effect of air pollution. Tertiles of NDVI, personal PM_{2.5} exposure, and personal ozone exposure were used in these analyses.

Results We found positive associations of CO and ozone personal exposure, respectively, with percent change of the three oxidative stress biomarkers. The association tended to be significant only in the ozone model with the percent change of 8-OHdG [8.69% 95%CI: (2.98,14.39), p-value=0.004]. However, in the models of ambient air pollution, some non-significantly negative associations were observed. Consistent positive associations of ambient lag 1- and 2- day CO

exposure with the percent change in levels of each of the three oxidative stress biomarkers were weakly persisted. However, the positive associations remained significant between CO exposure and total MDA (p value=0.033) only in lag2-day. In the analyses of greenness as the exposure variable, we observed that individuals who lived in greener areas tended to have lower levels of oxidative stress. Participants in the highest NDVI tertile (0.36-0.83) had significantly lower free and total MDA levels, mean and (95%CI) by -20.21% (-37.84%, -1.30%) and -17.77% (-32.89%, -2.16%), respectively, compared to the lowest NDVI tertile (0.11-0.25) (p-value =0.028). In the urban area, we found significant negative associations of NDVI with free MDA (p=0.003), total MDA (p =0.005), and 8-OHdG (p=0.022), but not in the peri-urban area. In the modification (interaction) analyses, we observed negative estimates of quantified NDVI associated with each of the three biomarkers in the low personal ozone exposure group (Ozone= \leq 18.7 ppb). We also observed negative estimates of quantified NDVI associated with free and total MDA in the low PM_{2.5} exposure group (PM_{2.5}= \leq 32 μ g/m³). In addition, we observed significant effects of personal ozone exposure on 8-OHdG [17.77 95%CI: (8.04, 27.56), p value=0.010]; personal CO exposure on free MDA [12.48 95%CI: (3.15, 21.85), p value=0.012 and total MDA [9.06 95%CI: (1.28, 16.64), p value=0.021] only in participants falling in the lowest NDVI tertile; and the positive associations were no longer significant in participants with higher tertiary NDVI.

Conclusion The protective effects of greenness on oxidative stress, especially in urban residents, elucidates the importance of green space in the urban built environment. Additionally, the adverse effects of air pollution exposure on oxidative stress indicates the noteworthiness of personal protection against air pollution exposure in urban residents.

Dedication

This thesis is far beyond the confines of written letters. Without the following people and team, this work would have never come true, and I would like to give my great acknowledgment to:

Dr. John. S. Ji, for two years of supervising my master's study, for coaching and editing my writing again and again, and being the role model of a researcher.

Dr. Junfeng (Jim) Zhang, for inspiring me to conduct these interesting findings and coaching through the writing process.

Dr. Abu Abdullah, for teaching me all the courses and the wise advice for the thesis.

Father, Dr. Liwei Qi, for enlightening the study in health and medicine.

Mother, Mrs. Naxin Xiao, for the always encouragement and support.

Ms. Liria Li, for both mental and academic support.

My classmates, who are also my friends.

Dr. Tong Zhu and Dr. Frank Kelly from the AIRLESS study team.

Mr. Yanbo Teng and Mr. Hailong Han from Dr. Jim Zhang's DKU Lab.

DKU Global Health Research Center and Environment Research Center.

Contents

Abstract.....	4
Dedication	7
List of Tables	10
1. Introduction	1
2. Methods	4
2.1 Study participants	4
2.2 Covariates	4
2.3 Outcome measurement: oxidative stress biomarkers	5
2.4 Contemporary greenness	6
2.5 Ambient and personal air pollution	6
2.6 Statistical analysis.....	7
3. Results.....	10
3.1 Population characteristics	10
3.2 Associations between personal and ambient air pollution with the percent change of oxidative stress biomarkers	13
3.3 Associations between contemporary NDVI with oxidative stress biomarkers.....	17
3.4 Modification effects of greenness and air pollution on oxidative stress biomarkers	21
4. Discussion	22
5. Limitations and Strengths.....	28
6. Public health implication	30
7. Conclusion.....	31

Appendix A.....	32
References.....	35

List of Tables

Table 1 Descriptive statistics for the 251 participants from the AIRLESS study	11
Table 2 Personal monitored and ambient monitored air pollution exposure levels	12
Table 3 The association of personal and ambient air pollution exposure with the percent change of oxidative stress biomarkers	14
Table 4 Lag effects of personal and ambient air pollution exposure in relation to the percent change of oxidative stress biomarkers	15
Table 5 Tertiary NDVI index in relation to the mean percent change of oxidative stress biomarker	18
Table 6 Subgroup analyses on the associations of contemporary greenness and oxidative stress biomarkers by 0.1 unit of NDVI index	19
Table 7 Air pollution modification analysis of association between greenness and oxidative stress biomarkers by 0.1 unit of NDVI index	20

1. Introduction

Urbanization is an ongoing phenomenon in developing countries, which coincides with rising urban pollution and decreasing natural habitats such as green space ("World Population Policies 2019," 2019). In Beijing, the capital city of China, this circumstance has made urban (districts within the Beijing Fifth Ring Road) and peri-urban (districts outside the Beijing Fifth Ring Road) spaces represent disparities in health facilities, environment, demography, residential health status, and even pollutant exposure profiles (Bai, Chen, & Shi, 2012). The city also has around 21.7 million permanent residents, making Beijing one of the most populous cities in the world. With complex urbanization dimensions, Beijing had an urban green coverage of 48.4% in 2016 and 2017 (*Beijing Statistical Yearbook 2020*, 2020). Notably, Beijing sets records for having some of the highest air pollution levels globally and has some unique air pollution features, e.g., central heating systems are mainly used in urban areas, while traditional biomass and coal energy is still the primary source in peri-urban areas. With PM_{2.5} steadily exceeding the Chinese air quality standards and the WHO air quality guidelines, the air pollution in this city accounts for a wide range of disease outcomes (Liang et al., 2019; Wang, Xu, et al., 2018). Simultaneously the land space of Beijing has evolved gradually. Exposure to a different level of residential greenness has been supported by much biological evidence on the negative association with air pollution.

Both air pollution and green space are essential urban environmental exposures to city-dwellers. Accumulating longitudinal data also indicates that a higher amount of residential greenness is associated with dementia (Astell-Burt, Navakatikyan, & Feng, 2020), sleep duration (Astell-Burt, Feng, & Kolt, 2013), serum 25(OH)D concentrations (Ji et al., 2019), activities of daily living

(ADL) (Peng et al., 2020) and a range of health outcomes. Also, existing persuasive evidence supports that air pollution is one of the leading risk factors for mortality (Dedoussi, Eastham, Monier, & Barrett, 2020; Dockery et al., 1993) and one of the most researched factors for cardio-pulmonary diseases (Wang, Bi, & Olde Rikkert, 2018; Weissmann, 2018). Previous environmental epidemiological studies used regional ambient data to estimate the air pollution exposure in Beijing (Liang et al., 2019; H. Zhang et al., 2020), which may not accurately capture personal exposure. Studies have also supported the significant difference between personal exposure with regional ambient exposure (Y. Han et al., 2020). Simultaneously, there needs to be a better understanding of how the individual exposure in relation to the population health effects. Furthermore, air pollution components are associated with urban areas' geographic spatial differences, like fine particulate, nitrogen oxides, and carbon monoxide. Evidence also supports the air pollution level is significantly higher in urban areas than in rural or peri-urban areas (Yiqun Han et al., 2020; Nunes, Branco, Alvim-Ferraz, Martins, & Sousa, 2015). On the other hand, residential greenness, which represents plant and vegetation coverage, is also attributed to regional features (D. L. Crouse et al., 2019; Dan L. Crouse et al., 2017; Ji et al., 2019).

There are still uncertainties in our understanding of biomarkers reflecting and mechanisms underlying the health effects of air pollution exposure and those of insufficient greenness exposure. This is attributable to insufficient research on potential biological pathways underlying residential greenness with air pollution exposure. Oxidative stress is a common pathological pathway linking environmental exposure and adverse health outcomes. However, the relationship between greenness exposure and oxidative stress is poorly understood. To our knowledge, we conducted the first study that focused on the effects of personal air pollutant exposure and greenness on oxidative stress. This study has the following aims: (1) To investigate the

association of personal and ambient air pollution exposure with oxidative stress biomarkers and the lag effects of air pollution on oxidative stress. (2) To explore the association between tertiary NDVI with oxidative stress and the robustness of the effects. (3) To study whether air pollution exposure modifies the effect of greenness and whether greenness modifies the effect of air pollution.

2. Methods

2.1 Study participants

This study was developed from the Effects of AIR pollution on cardiopuLmonary disEaSe in urban and peri-urban reSidents in Beijing (AIRLESS) study. The study design, protocol, inclusion, and exclusion criteria are described elsewhere (Yiqun Han et al., 2020). In this panel study, 123 urban and 128 peri-urban non-smoking participants over 49 years of age were recruited from two well-established cohorts in Beijing. Each participant was trained to carry a personal air monitor (PAM) to measure gaseous air pollutants and chemical and physical fine particles on seven consecutive days during winter 2016 (7th November to 21st December) and summer 2017 (22nd May to 21st June). All participants received standardized physical examinations on urinary oxidative stress biomarker levels at each examination visit, and data on demographics, health status, and lifestyle were collected via questionnaires contemporarily. All participants signed the written informed consent for the AIRLESS study. The Institutional Review Board approved the study IRB of the Peking University, China (IRB00001052-16028), and the College Research Ethics Committee of King's College London, UK (HR-16/17-3901).

2.2 Covariates

Based on the latest follow-up questionnaire, demographic variables included age, gender, education levels (never went to school, primary school, middle & high school and college & university or beyond), examination seasons (summer and winter), residential sites (urban and peri-urban), and household stove number. Anthropometric covariates were body mass index (BMI) and waist-hip ratio, which were associated with oxidative stress in previous studies (Rodríguez-San Nicolás, SÁnchez-Rodríguez, Zacarías-Flores, Correa-Muñoz, & Mendoza-

Núñez, 2020). Lifestyle variables were weekly drinking frequency, previous smoking status (former smoker and never smoked), and weekly outdoor activity frequency. The criteria of this study excluded smokers. The participants were non-smokers or those who had quit smoking longer than three years ago. In addition, disease status was considered, because some clinically diagnosed diseases were strongly associated with oxidative stress, including diabetes and hypertension (Graille et al., 2020; Yeager et al., 2018). Hypertension was documented in two repeated measurements based on systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Diabetes was documented on behalf of the doctor's diagnosis, participants who answered 'do not know' were assigned into the non-diabetic group.

2.3 Outcome measurement: oxidative stress biomarkers

Multiple urinary oxidative stress biomarkers and urinary specific gravity were collected and measured at each examination, including urinary creatinine, urinary free and total malondialdehyde (MDA, ng/ml), and urinary 8-hydroxydeoxyguanosine (8-OHdG, ng/ml). Measured free MDA, total MDA, and 8-OHdG were adjusted by urinary creatinine, and the levels of the three adjusted biomarkers were ln-transformed due to right skewness.

We also calculated the percent change in levels of the three urinary oxidative stress biomarkers between the two clinical examinations within one season $[(\text{Second examination value} - \text{First examination value}) / \text{First examination value}]$ to explore the changing degree of urinary oxidative stress.

2.4 Contemporary greenness

We calculated the daily matched NDVI value of winter 2016 (7th November to 21st December) and summer 2017 (22nd May to 21st June) by the PAM carrying dates of each participants. greenness levels by the daily average satellite-derived normalized difference vegetation index (NDVI) in the zone with 500m*500m grids in Google Earth Engine (GEE) by the Moderate-resolution Imaging Spectroradiometer (MODIS) dataset from the National Aeronautics and Space Administration (NASA) ("Google Earth Engine," ; NASA). Owing to lack of personal address data, we used the coordinates of the ambient air pollution monitoring stations [coordinate points: the Peking University Urban Atmosphere Environment (PKUERS), the Institute of Atmospheric Physics (IAP), and the center of *Xibaidian Village*] and PAM carrying dates to match the greenness levels. NDVI is a parameter derived from the ratio of red to infrared light reflected from sunlight into space and represents photosynthesis activity. Contemporary NDVI values in Beijing ranged from 0.105 (representing low vegetation) to 0.834 (representing a high forest cover concentration). GEE was used to quantify the contemporary residential NDVI into the regional average level.

2.5 Ambient and personal air pollution

The PKUERS and the IAP measured the ambient urban daily air pollution average; and a newly established infrastructure in the *Xibaidian Village*, Pinggu District measured the ambient peri-urban daily air pollution average, respectively. Gaseous air pollutants (CO, NO, NO₂, and ozone) and fine particles (PM_{2.5}) were collected and documented by those monitoring stations daily.

The PAM was applied to collect personal air pollution exposure levels, the methodology and the settings are described elsewhere (Chatzidiakou et al., 2020). The PAM machine was deployed in

a well-protected and easy-to-use way, and all of the participants were instructed to carry the PAM for one week in company with their daily activities. The PAM measured the personal gaseous air pollution levels (CO, NO, NO₂, and ozone) and fine particles (PM₁ and PM_{2.5}) and PM₁₀ at a daily average level. The relative temperature, relative humidity, and relative wind speed were derived from the PAM with an algorithm.

2.6 Statistical analysis

We reported medians with quartiles for continuous variables and counts with percentages for categorical variables to describe the participants' baseline statistics. Also, medians with quartiles for the NDVI value to describe the participants' baseline residential greenness statistics. We used R software (version 3.6.1) to conduct all the analyses. Estimated changes were reported with 95% CIs, the confidence interval did not contain 0, and $p < 0.05$ was considered statistically significant in this study.

To explore the association of personal and ambient air pollution exposures with urinary oxidative stress levels, we first used the lmerTest package to perform the association between the mean of personal and ambient air pollution exposures, respectively, with the percent change of urinary oxidative stress biomarkers. Models were estimated using linear mixed-effects models adjusted for urinary specific gravity, demographic covariates (age, gender, education levels, household stove number, examination seasons, sites, body mass index, and waist-hip ratio), lifestyle covariates (drinking habits, previous smoking status) and environment covariates (relative humidity, relative temperature, and wind speed). For the environment covariates, in the personal air pollution exposure models, we adjusted for the individual relative temperature and humidity;

in the ambient air pollution models, we adjusted for the regional average temperature and humidity. Meanwhile, the distributed lag linear model was then used to explore the hysteresis effects of the daily air pollution exposure. The models were adjusted for the same covariates as previous analysis and performed by `dlnm` package in R.

In the analyses of greenness as the exposure variable, we divided the previous calculated contemporary NDVI value into tertiles based on its distribution in both urban areas and peri-urban areas. We conducted the tests by establishing each tertile's median value as the continuous NDVI value variable to reduce the extreme value effects on the linear trends in different models. The linear mixed-effects model was used to estimate the associations of tertiary NDVI with free MDA, total MDA, and 8-OHdG, respectively. We adjusted for demographic covariates (age, gender, education levels, examination seasons, sites, household stove number, BMI, and waist-hip ratio), the urinary specific gravity, and environmental covariates (relative temperature, relative humidity, and wind speed) in the model 1. Additionally, we created a model 2 that included adjustments for demographic covariates, lifestyle covariates (previous smoking status and drinking frequency), and morbidity covariates (diabetes and hypertension). Then, a fully-adjusted model that included all of the above covariates was developed (model 3). Besides, subgroup analysis was used for the association between quantified NDVI with the mean percent change of oxidative stress biomarkers separately to explore whether the association varied in sites (urban and peri-urban), gender (male and female), hypertension (41.5%), diabetes (17.2%), outdoor activity frequency (less than three times per week and more than four times per week) by using the linear mixed-effects model and adjusting for the demographic, lifestyle, morbidity and environment covariates.

Finally, to explore the interaction between greenness and air pollution in affecting oxidative stress by each of these exposure variables, stratified analysis was used to examine whether air pollution exposure modifies the effect of greenness and whether greenness modifies the effect of air pollution. Tertiary NDVI, personal PM_{2.5} exposure, and personal ozone exposure were used in these analyses. We first explored whether the negative association of contemporary greenness with oxidative stress altered in different exposure matrices. We performed the linear mixed-effects regressions separately in varied personal ozone exposure levels (<18.7ppb and ≥18.7 ppb) and personal PM_{2.5} exposure levels (≤32μg/m³ and >32μg/m³) by adding an interaction term to these models. In the following analysis, stratified linear mixed-effects regressions were utilized to the modification effects of greenness on air pollution. NDVI value was stratified into three levels (1st NDVI: 0.105-0.249; 2nd NDVI: 0.249-0.357; 3rd NDVI: 0.357-0.834), and then we coded the regression models of ambient and personal air pollutant exposure levels with the percent change of oxidative stress biomarkers in each tertile of NDVI, respectively.

3. Results

3.1 Population characteristics

Table 1 describes the distribution of population characteristics, including all the levels of oxidative stress biomarkers, demographic, comorbidity, and lifestyle variables in urban and peri-urban sites. Study participants had a median age of 65 (P₂₅: 62, P₇₅: 70) in the urban area and 61 (P₂₅: 56.75, P₇₅: 65) in the peri-urban area. The median of urinary free MDA [urban: 1152.53 ng/ml, peri-urban: 989.73 ng/ml], total MDA [urban: 8453.84 ng/ml, peri-urban: 8279.36 ng/ml], 8-OHdG [urban: 4.28 ng/ml, peri-urban: 2.54 ng/ml], and creatinine [urban: 4.54 ng/ml, peri-urban: 3.95 ng/ml] levels were lower in the peri-urban area than the urban area; the median of quantified NDVI [urban: 0.23, peri-urban: 0.31] were higher in the peri-urban area than the urban area.

The personal air pollution exposure of NO, NO₂, ozone, and fine particles (PM₁, PM_{2.5}, and PM₁₀) levels of urban residents were significantly lower than peri-urban residents (Table 2). In addition, the median ambient CO and ambient NO₂ exposure levels of peri-urban residents were also relatively lower than urban residents (Table 2).

Table 1 Descriptive statistics for the 251 participants from the AIRLESS study

Characteristic N (%) or Median [P ₂₅ , P ₇₅]		Peri-urban (N=128)	Urban (N=123)	P-value
Age		61.00 [56.75, 65.00]	65.00 [62.00, 70.00]	<0.001
Gender	Male	51 (39.84)	59 (47.97)	0.219
	Female	77 (60.16)	63 (51.22)	
	Missing	0 (0.00)	1 (0.81)	
Education	Never went to school	15 (11.72)	0 (0.00)	<0.001
	Primary school	39 (30.47)	1 (0.81)	
	Middle and high school	74 (57.81)	26 (21.14)	
	College, university & beyond	0 (0.00)	95 (77.24)	
	Missing	0 (0.00)	1 (0.81)	
Number of household stove		2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.027
Smoking	Ex-smoker	29 (22.66)	24 (19.51)	0.673
	Never smoked	99 (77.34)	98 (79.67)	
Weekly drinking frequency		1.00 [1.00, 4.00]	4.00 [1.00, 5.00]	<0.001
BMI (kg/m²)		26.05 [24.33, 28.43]	24.62 [22.47, 26.95]	<0.001
WHR		0.89 [0.87, 0.93]	0.87 [0.84, 0.91]	<0.001
Hypertension	Non-hypertension	81 (63.28)	66 (53.66)	0.156
	Hypertension	47 (36.72)	57 (46.34)	
Diabetes	Non-diabetes	108 (84.38)	86 (69.92)	0.231
	Diabetes	20 (15.63)	37 (30.08)	
Outdoor activities frequency		3.00 [1.00, 5.00]	4.00 [2.00, 5.00]	0.308
NDVI		0.31 [0.28, 0.33]	0.23 [0.17, 0.24]	<0.001
Urinary creatinine (ng/ml)		3.95 [3.45, 4.52]	4.54 [3.21, 5.25]	0.014
Urinary specific gravity		1.01 [1.01, 1.02]	1.01 [1.00, 1.01]	<0.001
Urinary free MDA (ng/ml)		989.73 [756.19, 1379.14]	1152.53 [835.43, 1389.66]	0.164
Urinary total MDA (ng/ml)		8279.36 [6597.64, 10333.88]	8453.84 [5961.79, 11755.06]	0.829
Urinary 8-OHdG (ng/ml)		2.54 [1.58, 4.67]	4.28 [2.19, 7.58]	<0.001

BMI: Body Mass Index; WHR: Waist Hip Ratio. P-value was calculated using the Wilcox test and Chi-test.

Table 2 Personal monitored and ambient monitored air pollution exposure levels

Exposure	Peri-urban Median [P₂₅, P₇₅]	Urban Median [P₂₅, P₇₅]	P-value
Personal Exposure			
Adjusted Temperature (°C)	18.46 [11.89, 24.53]	22.19 [19.43, 26.06]	<0.001
Adjusted Relative Humidity (%)	47.55 [40.71, 54.89]	38.95 [31.13, 47.31]	<0.001
CO (ppm)	1.32 [0.57, 3.65]	1.48 [0.71, 3.61]	0.001
NO (ppb)	28.67 [17.37, 56.01]	46.37 [23.13, 92.11]	<0.001
NO ₂ (ppb)	6.53 [3.43, 11.05]	13.07 [7.43, 20.59]	<0.001
O ₃ (ppb)	3.49 [1.71, 8.63]	3.39 [1.60, 8.32]	0.054
PM ₁ (µg/m ³)	15.41 [4.60, 37.14]	11.49 [3.86, 24.05]	<0.001
PM _{2.5} (µg/m ³)	34.77 [22.42, 58.08]	25.23 [15.17, 39.17]	<0.001
PM ₁₀ (µg/m ³)	72.69 [48.43, 106.78]	51.02 [32.86, 76.22]	<0.001
Ambient Exposure			
Temperature (°C)	6.91 [0.84, 24.09]	7.81 [2.87, 25.28]	<0.001
Humidity (%)	53.14 [43.91, 72.99]	40.12 [32.03, 50.58]	<0.001
CO (ppm)	0.41 [0.20, 0.85]	1.12 [0.78, 1.52]	<0.001
NO (ppb)	277.67 [135.30, 304.55]	201.05 [162.58, 222.66]	<0.001
NO ₂ (ppb)	530.29 [400.54, 1251.05]	755.19 [450.03, 2620.90]	<0.001
O ₃ (ppb)	7.39 [4.61, 36.25]	9.33 [2.97, 61.64]	0.782
PM _{2.5} (µg/m ³)	16.78 [13.35, 26.16]	29.86 [22.43, 45.78]	<0.001

P-value was calculated using Wilcox test

3.2 Associations between personal and ambient air pollution with the percent change of oxidative stress biomarkers

The associations of CO, NO, NO₂, ozone, and particulate matters with the percent change in free MDA, total MDA, and 8-OHdG (Percent change of biomarkers: the second examination visit levels to the first and the fourth examination visit levels to the third) are shown separately for personal exposure and ambient exposure in Table 3. Among personal air pollution models, we found positive associations of CO and ozone exposure with the percent change of free MDA (CO 2.29%, ozone 0.40%), total MDA (CO 3.17%), and 8-OHdG (CO 3.12%, ozone 8.69%), respectively. The association tended to be significant only in the personal ozone exposure model with the percent change of 8-OHdG [8.69%, 95%CI: (2.98%, 14.39%), p-value=0.004].

Table 4 compares associations of oxidative stress biomarkers percent change with lag0-, lag1- and lag2-day air pollution exposure levels. We observed weakly but consistent positive associations of ambient lag 1- and 2- day CO exposure with the percent change of free MDA (lag1-day:1.05%, lag2-day: 1.48%), total MDA (lag1-day: 2.06%, lag2-day: 4.75%), and 8-OHdG (lag1-day: 6.81%, lag2-: 5.75%), respectively. However, the positive association remained significant only in the lag2-day CO exposure lag effect on total MDA (4.75%, 95%CI: (0.12%, 8.85%), p-value=0.033).

Table 3 The association of personal and ambient air pollution exposure with the percent change of oxidative stress biomarkers

Exposure	Percent change of Free MDA (95%CI)		P-value	Percent change of total MDA (95%CI)		P-value	Percent change of 8-OHdG (95%CI)		P-value
Personal Exposure									
CO (ppm)	2.29	(-2.25, 6.83)	0.337	3.17	(-0.19, 6.56)	0.075	3.12	(-9.51, 15.75)	0.638
NO (ppb)	-0.04	(-0.35, 0.28)	0.814	0.05	(-0.19, 0.28)	0.705	-0.37	(-1.24, 0.51)	0.426
NO ₂ (ppb)	-0.42	(-1.82, 0.99)	0.575	-0.43	(-1.47, 0.62)	0.432	3.78	(-0.01, 7.57)	0.058
O ₃ (ppb)	0.40	(-1.67, 2.47)	0.716	0.10	(-1.41, 1.68)	0.898	8.69	(2.98, 14.39)	0.004
PM ₁ (µg/m ³)	-0.59	(-1.32, 0.14)	0.122	0.03	(-0.51, 0.58)	0.908	-1.21	(-3.24, 0.82)	0.256
PM _{2.5} (µg/m ³)	-0.09	(-0.45, 0.27)	0.624	0.16	(-0.10, 0.43)	0.251	-0.78	(-1.77, 0.21)	0.132
PM ₁₀ (µg/m ³)	-0.06	(-0.31, 0.19)	0.661	0.12	(-0.07, 0.31)	0.238	-0.59	(-1.29, 0.12)	0.112
Ambient Exposure									
CO (ppm)	-25.68	(-57.98, 6.7)	0.135	2.65	(-19.71, 24.93)	0.823	-74.29	(-177.53, 21.28)	0.160
NO (ppb)	-0.41	(-1.37, 0.52)	0.415	-0.3	(-0.95, 0.35)	0.388	-2.51	(-5.53, 0.27)	0.104
NO ₂ (ppb)	-2.37	(-5.27, 0.45)	0.119	0.17	(-1.82, 2.13)	0.875	-6.3	(-15.49, 2.10)	0.178
O ₃ (ppb)	0.38	(-0.76, 1.52)	0.529	-0.5	(-1.28, 0.29)	0.234	-0.02	(-3.57, 3.43)	0.991
PM _{2.5} (µg/m ³)	-0.26	(-0.57, 0.05)	0.112	0.04	(-0.17, 0.25)	0.717	-0.76	(-1.74, 0.15)	0.131

Table 4 Lag effects of personal and ambient air pollution exposure in relation to the percent change of oxidative stress biomarkers

Exposure	Percent change of Free MDA (95%CI)		P-value	Percent change of total MDA (95%CI)		P-value	Percent change of 8-OHdG (95%CI)		P-value
Personal Exposure									
Lag0									
CO (ppm)	-0.64%	(-2.47%, 1.25%)	0.511	-0.48%	(-2.12%, 1.24%)	0.583	-1.49%	(-4.60%, 1.67%)	0.364
NO (ppb)	0.02%	(-0.05%, 0.07%)	0.631	0.01%	(-0.05%, 0.06%)	0.829	-0.06%	(-0.16%, 0.04%)	0.294
NO ₂ (ppb)	0.02%	(-0.53%, 0.57%)	0.947	0.12%	(-0.39%, 0.61%)	0.642	-0.60%	(-1.53%, 0.33%)	0.219
O ₃ (ppb)	-0.15%	(-0.82%, 0.53%)	0.671	-0.01%	(-0.60%, 0.63%)	0.978	0.22%	(-0.94%, 1.34%)	0.713
PM ₁ (µg/m ³)	0.18%	(-0.05%, 0.40%)	0.128	0.11%	(-0.09%, 0.31%)	0.288	0.23%	(-0.14%, 0.61%)	0.247
PM _{2.5} (µg/m ³)	0.01%	(-0.10%, 0.12%)	0.849	-0.02%	(-0.11%, 0.08%)	0.722	0.02%	(-0.15%, 0.20%)	0.834
PM ₁₀ (µg/m ³)	0.01%	(-0.07%, 0.09%)	0.746	0.00%	(-0.08%, 0.06%)	0.908	0.04%	(-0.09%, 0.17%)	0.588
Lag1									
CO (ppm)	-1.51%	(-3.19%, 0.12%)	0.079	-0.67%	(-2.21%, 0.83%)	0.400	-3.43%	(-6.23%, -0.46%)	0.022
NO (ppb)	0.00%	(-0.10%, 0.11%)	0.941	0.01%	(-0.09%, 0.10%)	0.884	0.01%	(-0.18%, 0.19%)	0.952
NO ₂ (ppb)	0.04%	(-0.43%, 0.52%)	0.881	-0.19%	(-0.62%, 0.26%)	0.415	-0.06%	(-0.89%, 0.77%)	0.887
O ₃ (ppb)	-0.02%	(-0.59%, 0.63%)	0.958	-0.30%	(-0.82%, 0.30%)	0.306	-0.54%	(-1.62%, 0.48%)	0.323
PM ₁ (µg/m ³)	0.19%	(-0.04%, 0.40%)	0.112	0.11%	(-0.10%, 0.31%)	0.321	0.04%	(-0.34%, 0.44%)	0.826
PM _{2.5} (µg/m ³)	0.02%	(-0.10%, 0.13%)	0.756	0.01%	(-0.10%, 0.12%)	0.841	-0.09%	(-0.29%, 0.11%)	0.377
PM ₁₀ (µg/m ³)	0.00%	(-0.08%, 0.09%)	0.923	0.01%	(-0.07%, 0.08%)	0.864	-0.02%	(-0.16%, 0.13%)	0.832
Lag2									
CO (ppm)	-1.10%	(-2.82%, 0.59%)	0.213	-0.23%	(-1.77%, 1.38%)	0.783	-2.08%	(-4.98%, 0.98%)	0.180
NO (ppb)	0.03%	(-0.09%, 0.14%)	0.619	0.04%	(-0.06%, 0.15%)	0.446	0.00%	(-0.20%, 0.19%)	0.994

NO ₂ (ppb)	-0.03%	(-0.50%, 0.48%)	0.923	0.02%	(-0.43%, 0.48%)	0.930	-0.06%	(-0.91%, 0.80%)	0.897
O ₃ (ppb)	-0.19%	(-0.76%, 0.43%)	0.538	-0.47%	(-0.99%, 0.10%)	0.091	0.33%	(-0.72%, 1.34%)	0.543
PM ₁ (µg/m ³)	0.01%	(-0.21%, 0.22%)	0.923	0.00%	(-0.20%, 0.20%)	0.993	-0.15%	(-0.52%, 0.24%)	0.446
PM _{2.5} (µg/m ³)	-0.09%	(-0.20%, 0.02%)	0.116	-0.06%	(-0.16%, 0.04%)	0.249	-0.13%	(-0.31%, 0.06%)	0.177
PM ₁₀ (µg/m ³)	-0.03%	(-0.11%, 0.05%)	0.521	-0.03%	(-0.11%, 0.04%)	0.384	-0.09%	(-0.23%, 0.06%)	0.234

Ambient Exposure

Lag0									
CO (ppm)	-4.67%	(-11.04%, 1.21%)	0.141	-3.04%	(-8.87%, 2.19%)	0.286	2.91%	(-7.90%, 12.77%)	0.586
NO (ppb)	-0.27%	(-0.49%, -0.06%)	0.017	-0.16%	(-0.36%, 0.03%)	0.115	-0.02%	(-0.39%, 0.34%)	0.920
NO ₂ (ppb)	-0.60%	(-1.06%, -0.17%)	0.009	-0.43%	(-0.86%, -0.05%)	0.038	-0.10%	(-0.87%, 0.63%)	0.797
O ₃ (ppb)	0.04%	(-0.38%, 0.44%)	0.862	-0.10%	(-0.46%, 0.27%)	0.610	-0.06%	(-0.77%, 0.62%)	0.859
PM _{2.5} (µg/m ³)	-0.01%	(-0.10%, 0.08%)	0.814	-0.03%	(-0.11%, 0.05%)	0.532	-0.06%	(-0.22%, 0.09%)	0.417
Lag1									
CO (ppm)	1.05%	(-3.91%, 5.45%)	0.662	2.06%	(-2.61%, 6.03%)	0.349	6.81%	(-1.82%, 14.51%)	0.104
NO (ppb)	0.01%	(-0.18%, 0.18%)	0.954	0.04%	(-0.13%, 0.20%)	0.605	0.16%	(-0.17%, 0.45%)	0.319
NO ₂ (ppb)	-0.20%	(-0.57%, 0.15%)	0.288	0.05%	(-0.31%, 0.36%)	0.757	0.48%	(-0.18%, 1.08%)	0.136
O ₃ (ppb)	0.14%	(-0.16%, 0.46%)	0.367	-0.16%	(-0.43%, 0.14%)	0.280	-0.75%	(-1.28%, -0.20%)	0.008
PM _{2.5} (µg/m ³)	0.03%	(-0.04%, 0.10%)	0.411	0.00%	(-0.07%, 0.06%)	1.00	-0.04%	(-0.17%, 0.08%)	0.501
Lag2									
CO (ppm)	1.48%	(-3.51%, 6.06%)	0.549	4.75%	(0.12%, 8.85%)	0.033	5.75%	(-2.86%, 13.84%)	0.182
NO (ppb)	0.06%	(-0.11%, 0.22%)	0.517	0.20%	(0.05%, 0.35%)	0.009	0.14%	(-0.15%, 0.43%)	0.340
NO ₂ (ppb)	0.04%	(-0.33%, 0.37%)	0.834	0.36%	(0.03%, 0.66%)	0.028	0.21%	(-0.40%, 0.81%)	0.505
O ₃ (ppb)	-0.03%	(-0.34%, 0.27%)	0.834	-0.32%	(-0.59%, -0.05%)	0.021	-0.60%	(-1.13%, -0.07%)	0.028
PM _{2.5} (µg/m ³)	-0.02%	(-0.09%, 0.04%)	0.489	-0.02%	(-0.09%, 0.03%)	0.447	-0.09%	(-0.20%, 0.03%)	0.144

3.3 Associations between contemporary NDVI with oxidative stress biomarkers

We observed the mean of free MDA and total MDA decreased with increasing tertiles of NDVI, and the MDA levels of the highest tertile of NDVI were significantly different from those in the lowest tertile of NDVI in all three models (Table 5). For example, in the fully adjusted model, participants in the highest tertile of NDVI (0.36-0.83) had significantly lower free and total MDA levels, mean and (95%CI) by -21.32% (-38.91%, -2.38%) and -20.06% (-35.06%, -3.92%), respectively, compared to the lowest NDVI tertile (0.11-0.25) (p-value =0.026, 0.016, respectively). The 8-OHdG models only indicated a statistically significant lower level, mean and (95%CI) by -20.79% (-39.26%, -0.65%), -23.96% (-43.81%, -2.17%), and -22.37% (-40.56%, -0.72%), in the middle NDVI tertile compared to the lowest NDVI group in all the three models. However, the negative trend was no longer significant with increasing tertiary NDVIs values. Additionally, there was a non-statistically significant decrease of 8-OHdG level in participants falling in the highest NDVI tertile, mean and (95%CI) by 2.09% (-22.30%, 26.78%), -1.08% (-28.29%, 26.92%), and -2.53% (-27.35%, 22.88%) across all the three models compared to the lowest NDVI tertile. There was no evidence of effect modification by gender, hypertension, diabetes, and outdoor activity frequency. However, in the urban area, we found significant negative associations of contemporary NDVI with indexed Free MDA (p-value=0.003), total MDA (p-value=0.005), and 8-OHdG (p-value=0.022), respectively, but not in the peri-urban area (Table 6).

Table 5 Tertiary NDVI index in relation to the mean percent change of oxidative stress biomarker

NDVI group	Mean percent change of Free MDA 95%CI	P-value	Mean percent of total MDA 95%CI	P-value	Mean percent change of 8- OHdG 95%CI	P-value
Model 1: demographic and lifestyle covariates adjusted model						
NDVI1*	0 (reference)	-	0 (reference)	-	0 (reference)	-
NDVI2*	-12.44% (-24.69%, 1.28%)	0.056	-11.26% (-21.98%, 1.07%)	0.048	-20.79% (-39.26%, -0.65%)	0.037
NDVI3*	-20.21% (-37.84%, -1.30%)	0.032	-17.77% (-32.89%, -2.16%)	0.028	2.09% (-22.30%, 26.78%)	0.873
Trend	-	0.015	-	0.012	-	0.585
Model 2: environmental covariates adjusted model						
NDVI1*	0 (reference)	-	0 (reference)	-	0 (reference)	-
NDVI2*	-13.20% (-26.09%, 0.86%)	0.052	-13.19% (-24.54%, -0.53%)	0.027	-23.96% (-43.81%, -2.17%)	0.025
NDVI3*	-22.60% (-41.52%, -3.16%)	0.022	-19.97% (-35.93%, -2.88%)	0.020	-1.08% (-28.29%, 26.92%)	0.941
Trend	-	0.011	-	0.009	-	0.514
Model 3: full adjusted model						
NDVI1*	0 (reference)	-	0 (reference)	-	0 (reference)	-
NDVI2*	-12.89% (-25.03%, 1.23%)	0.053	-12.50% (-23.11%, 0.41%)	0.032	-22.37% (-40.56%, -0.72%)	0.030
NDVI3*	-21.32% (-38.91%, -2.38%)	0.026	-20.06% (-35.06%, -3.92%)	0.016	-2.53% (-27.35%, 22.88%)	0.850
Trend	-	0.011	-	0.008	-	0.486

*NDVI1: 0.11-0.25; *NDVI2: 0.25-0.36; NDVI3: 0.36-0.83

Table 6 Subgroup analyses on the associations of contemporary greenness and oxidative stress biomarkers by 0.1 unit of NDVI index

Subgroup	Estimate of total MDA (95%CI)		P-value	Estimate of free MDA (95%CI)		P-value	Estimate of 8-OHdG (95%CI)		P-value
Resident area									
Urban	-189.05	(-310.57, -53.90)	0.005	-35.90	(-58.56, -11.29)	0.003	-0.14	(-0.26, -0.02)	0.022
Peri-urban	4.62	(-8.25, 16.40)	0.473	-23.97	(-113.74, 63.05)	0.604	0.06	(-0.03, 0.15)	0.225
Gender									
Male	-0.52	(-19.39, 21.69)	0.961	-40.57	(-169.09, 97.8)	0.558	0.08	(-0.03, 0.19)	0.155
Female	-8.47	(-22.49, 5.55)	0.249	-4.76	(-87.45, 87.65)	0.917	0.01	(-0.08, 0.10)	0.863
Hypertension*									
Non-hypertension	-2.54	(-19.05, 14.59)	0.775	-36.74	(-138.03, 75.38)	0.506	0.02	(-0.08, 0.11)	0.752
Hypertension	-8.24	(-25.21, 9.24)	0.366	-51.20	(-153.82, 53.06)	0.347	0.04	(-0.08, 0.15)	0.525
Diabetes*									
Non-diabetes	-0.51	(-14.11, 12.81)	0.942	-17.10	(-97.81, 61.69)	0.679	0.08	(-0.01, 0.16)	0.076
Diabetes	-5.20	(-32.41, 22.01)	0.726	-140.54	(-371.32, 89.74)	0.262	-0.09	(-0.26, 0.08)	0.327
Outdoor activities frequency									
Less than 3 times/week	-3.63	(-18.29, 10.64)	0.633	-24.83	(-111.68, 64.59)	0.589	0.04	(-0.05, 0.12)	0.420
More than 4 times/week	-8.67	(-30.89, 11.34)	0.420	-67.17	(-194.72, 79.50)	0.341	0.04	(-0.08, 0.17)	0.502

*Hypertension and diabetes status were based on doctor's diagnosis

Table 7 Air pollution modification analysis of association between greenness and oxidative stress biomarkers by 0.1 unit of NDVI index

Air pollution	Estimate of creatinine adjusted total MDA (95%CI)			Estimate of creatinine adjusted free MDA (95%CI)			Estimate of creatinine adjusted 8-OHdG (95%CI)		
			p- value			p- value			p- value
Personal Ozone exposure									
personal Ozone ≤ 18.7 ppb	-17.61	(-37.91, 4.13)	0.109	-98.26	(-206.25, 16.33)	0.089	-0.03	(-0.16, 0.11)	0.695
personal Ozone >18.7 ppb	1.11	(-13.94, 14.59)	0.882	3.55	(-97.44, 101.68)	0.946	0.04	(-0.03, 0.11)	0.288
Personal Pm2.5 exposure									
personal PM _{2.5} ≤32 µg/m ³	-13.66	(-32.23, 4.48)	0.158	-76.00	(-185.35, 33.88)	0.186	0.0947	(-0.01, 0.19)	0.056
personal PM _{2.5} > 32 µg/m ³	4.38	(-10.49, 18.53)	0.566	-6.75	(-103.34, 92.88)	0.895	-0.0359	(-0.14, 0.07)	0.515

3.4 Modification effects of greenness and air pollution on oxidative stress biomarkers

First, we observed negative estimates of 0.1 unit quantified-contemporary NDVI in the lower personal ozone exposure group ($Ozone \leq 18.7$ ppb) on free MDA (-98.26), total MDA (-17.61), and 8-OHdG (-0.03); and in the lower personal $PM_{2.5}$ exposure group ($PM_{2.5} \leq 32$ $\mu g/m^3$) on free MDA (-76.00) and total MDA (-13.66), respectively (Table 7).

Previously we found non-significant positive associations of personal CO and ozone exposure levels with the percent change of free MDA, total MDA, and 8-OHdG, separately. To verify the result's robustness, we included NDVI into the analyses and stratified participants by the NDVI tertiles. The association then became significant of personal CO exposure with the percent change of free MDA [12.48 95%CI: (3.15, 21.85), p value=0.012] and total MDA [9.06 95%CI: (1.28, 16.64), p value=0.021]; and of personal ozone exposure with the percent change of 8-OHdG [17.77 95%CI: (8.04, 27.56), p value=0.010] only in participants falling in the lowest NDVI tertile. The associations were no longer significant when the NDVI tertile increased (Appendix A).

4. Discussion

We found that increasing personal CO and ozone exposures were associated with significant positive changes of urinary 8-OHdG. The sensitive window for CO exposure lag effect on urinary 8-OHdG was lag two days. Also, we found residents who lived in an area with a higher greenness level to have lower levels of oxidative stress. Our results suggested a stronger negative association of contemporary greenness with oxidative stress biomarkers for urban residents but not peri-urban residents. In addition, only in participants falling in the lowest NDVI group (most-developed urban area), we observed negative associations of personal CO exposure with urinary MDA; and personal ozone exposure with the 8-OHdG persisted, but no longer significant with the tertiary NDVI increased.

Previous studies reported that the low contemporary greenness level and a range of subclinical and clinical traits were associated (Astell-Burt & Feng, 2019, 2020a, 2020b). Similarly, evidence supported the negative association between residential greenness and oxidative stress (Yeager et al., 2018). Although MDA and 8-OHdG were well-researched biomarkers on the acute antioxidative process against air pollution exposure (Cui et al., 2018; Ren, Fang, Wright, Suh, & Schwartz, 2011), very little was found in the literature review on the association of greenness and urinary oxidative stress, and whether air pollution exposure modifies the effect of greenness and whether greenness modifies the effect of air pollution.

To our knowledge, this study is the very first one to investigate the association between greenness with urinary MDA and 8-OHdG and the very first one to probe into the modification effects of air pollution exposure and greenness on urinary MDA and 8-OHdG, respectively. Although Crouse et al. and Yeager et al. found an association between decreasing mortality risks and increasing greenness in their community-based studies (D. L. Crouse et al., 2019; Yeager et al., 2018), and researches about the effects of air pollution on oxidative stress were well-studied (Saenen et al., 2019), little is known about the imbalanced pathways underlying the dynamic balance among greenness, air pollutants, and oxidative stress cycling. Therefore, findings of this study are novel and important as discussed below.

Pathophysiologically, gaseous and fine particulate air pollutants can be transported by the respiratory organs into the circulatory system through the bronchial capillary. The highly oxidizing pollutants could overburden the antioxidant defense of erythrocytes and initiate cellular DNA damage and organic inflammation. This imbalanced process disrupts the dynamic balance between the reactive oxygen species production and the antioxidant defense system, defined as oxidative stress cycling (Finkel & Holbrook, 2000; Liu et al., 2018; Ren et al., 2011). The cycling oxidative stress is characterized as increased endothelial permeability, which may trigger a series of pathophysiological processes such as endothelial dysfunction, changes in vascular tone, platelet adhesion and aggregation, and enhanced thrombosis.

As a well-researched biomarker, MDA indicates the oxidating polyunsaturated fatty acids, which is caused by lipid peroxidation due to acute air pollutants exposure (Cui et al., 2018; Gong et al., 2013). Therefore, the accumulation of lipid peroxidation products in blood vessel walls promotes

atherosclerosis, increases oxidative stress, inflammation, and risks to cardiovascular diseases (W. Li et al., 2016; Miller, 2014; Miller, Shaw, & Langrish, 2012). Bio-mechanically, Aslaner et al. found evidence that ozone exposure was positively associated with tissue MDA in rats (Aslaner et al., 2016); André et al. also reported a positive association of CO exposure and MDA levels in ventricular tissue of rats (André et al., 2011). He et al. reported positive associations between PM_{2.5} and ozone exposure with MDA (He, Cui, et al., 2020) on the populational scale. The synthesis of MDA is relatively independent of the digestive system effect, which also suggests MDA as a stable biomarker for evaluating oxidative stress (Z. Li, Liu, Xu, Guo, & Wu, 2020).

The urinary 8-OHdG generated in the circulatory system is sensitive to the acute initiation of deoxyribonucleic acid (DNA) damage (Graille et al., 2020; Ren et al., 2011). 8-OHdG also represents the most abundant DNA damage owing to the simple formation process and ease of mutation (Graczyk et al., 2016; Valavanidis, Vlachogianni, & Fiotakis, 2009). The fuel filling attendants were found to have higher 8-OHdG concentrations due to exposure to PM₁₀, benzene, total volatile organic compound, and CO compared to the control group without such exposure (Gaikwad, Mahmood, Beerappa, Karunamoorthy, & Venugopal, 2020). Prior studies supported that 8-OHdG is a widely used biomarker for DNA damage initiated by exogenous oxidative pollutants (Sajous, Botta, & Sari-Minodier, 2008; Valavanidis et al., 2009).

The association of oxidative stress biomarkers and air pollutants is variant. Zhang et al. found that the daily average of SO₂ was negatively associated with plasma MDA (G. Zhang et al., 2020); Siteb et al. also observed reserve association of Air Quality Index (AQI) and urinary MDA (Stieb et al., 2018). Contemporarily, Delfino et al. reported non-significant association between

measured air pollution levels with plasma inflammation and oxidative stress biomarkers (Delfino et al., 2008). Those inconsistent findings may not consider personal level air pollution exposure, as the significant differences between personal air pollution with ambient air pollution concentrations were observed in the previous AIRLESS study (Y. Han et al., 2020). Therefore, the personal level air pollution exposure could be a more robust indicator with higher reliability and validity than ambient level air pollution concentration serving as a proxy for personal exposure.

Additionally, we also detected the hysteresis effect of CO exposure on 8-OHdG. Although the blood hemoglobin has an efficient combination ability to CO, the dissociation period is much more extended than oxygen. A previous study also supported the lag effect of CO on cardiovascular diseases' health effects (Shah et al., 2015).

In Beijing, motor vehicles are considered one of the critical sources of gaseous air pollution in urban and peri-urban areas ("Beijing Municipal Bureau of Environmental Protection," 2016). Both the local traffic gas emissions and industrial waste emissions have contributed to the mass oxygenated air pollutants and fine particulate pollutants (Pan, Yao, & Yang, 2016). When we included personal CO exposure and personal ozone exposure in the regression models, a potential positive association between CO and ozone exposure with oxidative stress was observed, suggesting the source of pollutants matrix should be considered. For models using 8-OHdG as the independent variable, the strong association with ozone indicating the underlying potential utilization of 8-OHdG as a robust biomarker in the ozone pollution exposure study. This result

also consistent with the findings observed by Dengizek et al.(Seydanur Dengizek et al., 2019) and He et al.(He, Lin, et al., 2020).

Some researchers suggested that higher greenness surroundings could support lower clinical and subclinical traits by reducing air pollutants concentrations and increasing outdoor activities, while some researchers found associations between cardiovascular diseases with residential greenness after controlled by air quality (James, Banay, Hart, & Laden, 2015; Twohig-Bennett & Jones, 2018). Our study observed different result patterns in different NDVI groups, which allied with previous findings that the environmental factors could vary in areas with different NDVI (D. L. Crouse et al., 2019). We then adjusted for environmental covariates in the second model and both the demographic and environmental covariates in the third model; the associations were consistent across different models for each of the biomarkers. On this basis, our results supported the beneficial effects of contemporary greenness on reducing lipid peroxidation of oxidative stress.

In addition, our findings were consistent with the evidence observed in previous studies, which showed green space was negatively associated with COPD prevalence (Fan et al., 2020) and cancer risks (O'Callaghan-Gordo et al., 2018), especially in urban residents. That evidence supported our findings on the strong negative association of contemporary greenness with MDA and 8-OHdG in urban residents. Our result also indicated that, as one of the complexities of Beijing's urban sprawls (Zhao, Li, & Liu, 2020), vegetation and green space have substantial effects on urinary oxidative stress, especially in those who live in urban areas.

We also investigated the modification effect of greenness. In previous studies that directly examined the effect on the association between air pollution and mortality, they observed an association of PM_{2.5} with mortality decreased while residential greenness increased (D. L. Crouse et al., 2019; Kioumourtzoglou, Schwartz, James, Dominici, & Zanobetti, 2016). Owing to oxidative stress biomarkers were also used as predictors of mortality (Epifânio, Balbino, Ribeiro, Franceschini, & Hermsdorff, 2018), our finding supported that people living in the area with the lowest NDVI had a significant association of air pollutants with oxidative stress. Therefore, this may be attributable to the synergistic effects of poor vegetation coverage on environmental pollution exposure.

5. Limitations and Strengths

There are several strengths of this study. First, the air pollutant exposure data were measured on both ambient and personal level, the assessments of oxidative stress biomarkers, greenness, and air pollution data were performed separately. Second, we adjusted for demographic covariates, comorbidity covariates, lifestyle covariates, and individual or ambient meteorological covariates in the regression models. Third, to our knowledge, this is the first evidence investigating the association of residential greenness with urinary MDA and 8-OHdG and the first study to probe into the effects of personal air pollution and residential greenness on urinary MDA and 8-OHdG. Overall, our finding adds a new page of the current body of literature demonstrating the health benefits of living in greener areas and the contribution of green space in urban residents.

The study also has several limitations worth noting. First of all, the sample size of this study is relatively small, and there may be some selection bias. Those participants are predominantly Han Chinese individuals of Asian and mainly middle-aged and older adults, limiting the generalizability of our findings to other countries or other age groups. Second, the characteristic of greenness may differ with the same NDVI index. Therefore, the health effect of greenness may be different depending on the NDVI component is the grassland or tree canopy (Astell-Burt & Feng, 2020b). Our estimates of NDVI were assigned using 500m satellite buffers and coordinates of ambient air pollution monitoring stations, and there may be potential confounding of the greenness composition that we were unable to exclude. Also, a similar related limitation of this part of the study is that we used the community district's longitude and latitude to locate coordinates, which may introduce misclassification bias (different contemporary NDVI within the

same community). Thirdly, although this is a longitudinal study, the personal exposure monitor period is relatively short. Future studies should perform a longer follow-up. There is also potential confounding that we were unable to measure and to control in the statistical analyses. Lastly, we could not infer a causal relationship based on our study design.

6. Public health implication

The protective effects of greenness on oxidative stress in elderly residents in Beijing elucidates the fundamental role of green space construction in the urban planning and development process. Meanwhile, the health effects of personal air pollution exposure on oxidative stress also suggest the noteworthiness of personal protection against air pollution like facemasks and air purification systems, especially in the elderly population. Therefore, the green built environment should be incorporated into future studies on the air pollution health effects. Additionally, under the covid-19 pandemic situation, stakeholders and policymakers should then consider that facemasks are not only to prevent the spread of infectious diseases but also a meaningful way to reduce pollutant-induced oxidative stress.

7. Conclusion

Our study found a positive association between personal CO and ozone exposure and three oxidative stress biomarkers. We observed that residents who lived in an area with a higher greenness level had a lower concentration of oxidative stress biomarkers. Consistently, we also observed a negative association between contemporary greenness with oxidative stress biomarkers, especially in urban residents. Additionally, we observed positive associations of personal CO exposure with urinary MDA and personal ozone exposure with 8-OHdG only in participants falling in the lowest NDVI group. This study's findings add to the body of knowledge that residents with greener surroundings may have a better health status due to their lower levels of oxidative stress. The findings suggest that it is indispensable to consider built environment like greenness when studying air pollution health effects.

NDVI 2*	CO (ppm)	-0.51	(-4.92, 4.05)	0.822	0.53	(-2.48, 3.63)	0.733	3.80	(-7.94, 15.16)	0.513
	NO (ppb)	0.33	(-0.21, 0.87)	0.232	0.15	(-0.22, 0.52)	0.440	-0.65	(-2.07, 0.75)	0.367
	NO ₂ (ppb)	1.21	(-1.35, 3.82)	0.357	0.60	(-1.14, 2.29)	0.496	-0.84	(-7.31, 5.46)	0.796
	O ₃ (ppb)	0.60	(-2.15, 3.48)	0.667	0.85	(-1.41, 3.01)	0.412	1.65	(-5.76, 9.04)	0.665
	PM ₁ (µg/m ³)	-0.08	(-0.70, 0.55)	0.796	0.29	(-0.16, 0.74)	0.224	-1.29	(-3.02, 0.44)	0.156
	PM _{2.5} (µg/m ³)	-0.03	(-0.44, 0.39)	0.886	0.23	(-0.06, 0.51)	0.119	-0.61	(-1.66, 0.44)	0.266
	PM ₁₀ (µg/m ³)	0.05	(-0.26, 0.37)	0.766	0.19	(-0.03, 0.40)	0.079	-0.36	(-1.14, 0.42)	0.371
NDVI 3*	CO (ppm)	-2.80	(-21.72, 15.48)	0.766	10.86	(-0.94, 22.8)	0.074	-5.40	(-53.54, 42.73)	0.826
	NO (ppb)	-0.70	(-2.01, 0.62)	0.296	-0.17	(-1.06, 0.67)	0.698	-0.02	(-3.42, 3.38)	0.991
	NO ₂ (ppb)	1.32	(-1.49, 3.66)	0.269	0.35	(-1.20, 1.83)	0.643	6.22	(0.66, 11.20)	0.023
	O ₃ (ppb)	-1.41	(-4.44, 1.71)	0.375	-0.18	(-2.20, 2.00)	0.861	0.97	(-6.87, 8.82)	0.808
	PM ₁ (µg/m ³)	-3.81	(-15.27, 7.77)	0.527	-5.87	(-13.99, 3.15)	0.145	-28.17	(-55.97, -0.37)	0.049
	PM _{2.5} (µg/m ³)	-1.10	(-2.46, 0.27)	0.129	-0.56	(-1.51, 0.47)	0.242	-4.19	(-7.54, -0.83)	0.016
	PM ₁₀ (µg/m ³)	-0.88	(-1.65, -0.09)	0.036	-0.17	(-0.73, 0.42)	0.525	-2.51	(-4.41, -0.62)	0.010

Ambient Exposure

Overall	CO (ppm)	25.68	(-57.98, 6.70)	0.135	2.65	(-19.71, 24.93)	0.823	-74.29	(-177.53, 21.28)	0.160
	NO (ppb)	-0.41	(-1.37, 0.52)	0.415	-0.30	(-0.95, 0.35)	0.388	-2.51	(-5.53, 0.27)	0.104
	NO ₂ (ppb)	-2.37	(-5.27, 0.45)	0.119	0.17	(-1.82, 2.13)	0.875	-6.30	(-15.49, 2.10)	0.178
	O ₃ (ppb)	0.38	(-0.76, 1.52)	0.529	-0.50	(-1.28, 0.29)	0.234	-0.02	(-3.57, 3.43)	0.991

	PM _{2.5} (µg/m ³)	-0.26	(-0.57, 0.05)	0.112	0.04	(-0.17, 0.25)	0.717	-0.76	(-1.74, 0.15)	0.131
NDVI 1*	CO (ppm)	21.43	(4.06, 38.8)	0.017	27.81	(14.75, 40.78)	0.001	-4.65	(-40.79, 29.10)	0.781
	NO (ppb)	0.82	(0.01, 1.64)	0.063	1.13	(0.48, 1.78)	0.003	-0.42	(-1.81, 0.97)	0.602
	NO ₂ (ppb)	1.72	(0.41, 3.04)	0.011	1.99	(0.99, 2.99)	0.001	-0.39	(-3.24, 2.35)	0.777
	O ₃ (ppb)	-1.06	(-2.35, 0.21)	0.124	-1.38	(-2.46, -0.31)	0.021	1.00	(-1.11, 2.88)	0.428
	PM _{2.5} (µg/m ³)	0.35	(-0.05, 0.75)	0.106	0.60	(0.30, 0.90)	0.001	-0.33	(-1.14, 0.47)	0.422
NDVI 2*	CO (ppm)	3.62	(-18.33, 27.89)	0.757	5.92	(-11.49, 24.03)	0.528	-33.74	(-103.97, 34.66)	0.359
	NO (ppb)	0.04	(-0.69, 0.78)	0.913	-0.07	(-0.61, 0.51)	0.826	-1.24	(-3.42, 0.91)	0.288
	NO ₂ (ppb)	0.71	(-1.13, 2.58)	0.429	0.42	(-0.87, 1.72)	0.536	-2.73	(-7.64, 2.16)	0.288
	O ₃ (ppb)	-0.23	(-1.07, 0.60)	0.584	-0.43	(-1.08, 0.18)	0.215	0.23	(-2.38, 2.88)	0.868
	PM _{2.5} (µg/m ³)	-0.11	(-0.35, 0.14)	0.399	-0.04	(-0.23, 0.15)	0.718	-0.26	(-1.00, 0.49)	0.509
NDVI 3*	CO (ppm)	21.91	(-252.86, 126.11)	0.872	124.83	(-26.28, 289.23)	0.148	184.12	(-673.01, 305.15)	0.462
	NO (ppb)	-15.6	(-27.50, -2.59)	0.012	-10.50	(-18.08, -3.11)	0.007	-27.28	(-57.5, 2.94)	0.079
	NO ₂ (ppb)	3.68	(-0.56, 7.43)	0.055	0.90	(-1.62, 3.29)	0.465	7.97	(-1.27, 17.21)	0.093
	O ₃ (ppb)	1.87	(-1.21, 4.83)	0.167	1.05	(-0.58, 2.78)	0.190	0.11	(-4.00, 4.22)	0.958
	PM _{2.5} (µg/m ³)	2.19	(-0.39, 4.38)	0.040	0.90	(-0.37, 2.16)	0.153	0.49	(-3.45, 4.44)	0.808

*NDVI1: 0.11-0.25; *NDVI2: 0.25-0.36; NDVI3: 0.36-0.83

References

- André, L., Gouzi, F., Thireau, J., Meyer, G., Boissiere, J., Delage, M., . . . Cazorla, O. (2011). Carbon monoxide exposure enhances arrhythmia after cardiac stress: involvement of oxidative stress. *Basic Res Cardiol*, *106*(6), 1235-1246. doi:10.1007/s00395-011-0211-y
- Aslaner, A., Çakır, T., Tekeli, S., Avcı, S., Doğan, U., Tekeli, F., . . . Yılmaz, N. (2016). Medical ozone treatment ameliorates the acute distal colitis in rat. *Acta Cir Bras*, *31*(4), 256-263. doi:10.1590/s0102-865020160040000006
- Astell-Burt, T., & Feng, X. (2019). Association of Urban Green Space With Mental Health and General Health Among Adults in Australia. *JAMA Netw Open*, *2*(7), e198209. doi:10.1001/jamanetworkopen.2019.8209
- Astell-Burt, T., & Feng, X. (2020a). Does sleep grow on trees? A longitudinal study to investigate potential prevention of insufficient sleep with different types of urban green space. *SSM Popul Health*, *10*, 100497. doi:10.1016/j.ssmph.2019.100497
- Astell-Burt, T., & Feng, X. (2020b). Urban green space, tree canopy and prevention of cardiometabolic diseases: a multilevel longitudinal study of 46 786 Australians. *Int J Epidemiol*, *49*(3), 926-933. doi:10.1093/ije/dydz239
- Astell-Burt, T., Feng, X., & Kolt, G. S. (2013). Does access to neighbourhood green space promote a healthy duration of sleep? Novel findings from a cross-sectional study of 259 319 Australians. *BMJ Open*, *3*(8). doi:10.1136/bmjopen-2013-003094
- Astell-Burt, T., Navakatikyan, M. A., & Feng, X. (2020). Urban green space, tree canopy and 11-year risk of dementia in a cohort of 109,688 Australians. *Environ Int*, *145*, 106102. doi:10.1016/j.envint.2020.106102
- Bai, X., Chen, J., & Shi, P. (2012). Landscape urbanization and economic growth in China: positive feedbacks and sustainability dilemmas. *Environ Sci Technol*, *46*(1), 132-139. doi:10.1021/es202329f

Beijing Municipal Bureau of Environmental Protection. (2016). Retrieved from <http://www.bjepb.gov.cn>

Beijing Statistical Yearbook 2020. (2020).

Chatzidiakou, L., Krause, A., Han, Y., Chen, W., Yan, L., Popoola, O. A. M., . . . Jones, R. L. (2020). Using low-cost sensor technologies and advanced computational methods to improve dose estimations in health panel studies: results of the AIRLESS project. *J Expo Sci Environ Epidemiol*, *30*(6), 981-989. doi:10.1038/s41370-020-0259-6

Crouse, D. L., Pinault, L., Balram, A., Brauer, M., Burnett, R. T., Martin, R. V., . . . Weichenthal, S. (2019). Complex relationships between greenness, air pollution, and mortality in a population-based Canadian cohort. *Environ Int*, *128*, 292-300. doi:10.1016/j.envint.2019.04.047

Crouse, D. L., Pinault, L., Balram, A., Hystad, P., Peters, P. A., Chen, H., . . . Villeneuve, P. J. (2017). Urban greenness and mortality in Canada's largest cities: a national cohort study. *The Lancet Planetary Health*, *1*(7), e289-e297. doi:10.1016/s2542-5196(17)30118-3

Cui, X., Gong, J., Han, H., He, L., Teng, Y., Tetley, T., . . . Zhang, J. J. (2018). Relationship between free and total malondialdehyde, a well-established marker of oxidative stress, in various types of human biospecimens. *J Thorac Dis*, *10*(5), 3088-3097. doi:10.21037/jtd.2018.05.92

Dedoussi, I. C., Eastham, S. D., Monier, E., & Barrett, S. R. H. (2020). Premature mortality related to United States cross-state air pollution. *Nature*, *578*(7794), 261-265. doi:10.1038/s41586-020-1983-8

Delfino, R. J., Staimer, N., Tjoa, T., Polidori, A., Arhami, M., Gillen, D. L., . . . Sioutas, C. (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. *Environ Health Perspect*, *116*(7), 898-906. doi:10.1289/ehp.11189

- Dockery, D. W., Pope, C. A., 3rd, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., . . . Speizer, F. E. (1993). An association between air pollution and mortality in six U.S. cities. *N Engl J Med*, 329(24), 1753-1759. doi:10.1056/nejm199312093292401
- Epifânio, A. P. S., Balbino, K. P., Ribeiro, S. M. R., Franceschini, S. C. C., & Hermsdorff, H. H. M. (2018). Clinical-nutritional, inflammatory and oxidative stress predictors in hemodialysis mortality: a review. *Nutr Hosp*, 35(2), 461-468. doi:10.20960/nh.1266
- Fan, J., Guo, Y., Cao, Z., Cong, S., Wang, N., Lin, H., . . . Fang, L. (2020). Neighborhood greenness associated with chronic obstructive pulmonary disease: A nationwide cross-sectional study in China. *Environ Int*, 144, 106042. doi:10.1016/j.envint.2020.106042
- Finkel, T., & Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of ageing. *Nature*, 408(6809), 239-247. doi:10.1038/35041687
- Gaikwad, A. S., Mahmood, R., Beerappa, R., Karunamoorthy, P., & Venugopal, D. (2020). Mitochondrial DNA copy number and cytogenetic damage among fuel filling station attendants. *Environ Mol Mutagen*, 61(8), 820-829. doi:10.1002/em.22404
- Gong, J., Zhu, T., Kipen, H., Wang, G., Hu, M., Ohman-Strickland, P., . . . Zhang, J. J. (2013). Malondialdehyde in exhaled breath condensate and urine as a biomarker of air pollution induced oxidative stress. *J Expo Sci Environ Epidemiol*, 23(3), 322-327. doi:10.1038/jes.2012.127
- Google Earth Engine. Retrieved from <http://earthengine.google.org>
- Graczyk, H., Lewinski, N., Zhao, J., Sauvain, J. J., Suarez, G., Wild, P., . . . Riediker, M. (2016). Increase in oxidative stress levels following welding fume inhalation: a controlled human exposure study. *Part Fibre Toxicol*, 13(1), 31. doi:10.1186/s12989-016-0143-7
- Graille, M., Wild, P., Sauvain, J. J., Hemmendinger, M., Guseva Canu, I., & Hopf, N. B. (2020). Urinary 8-OHdG as a Biomarker for Oxidative Stress: A Systematic

Literature Review and Meta-Analysis. *Int J Mol Sci*, 21(11).
doi:10.3390/ijms21113743

Han, Y., Chatzidiakou, L., Yan, L., Chen, W., Zhang, H., Krause, A., . . . Kelly, F. J. (2020). Difference in ambient-personal exposure to PM_{2.5} and its inflammatory effect in local residents in urban and peri-urban Beijing, China: results of the AIRLESS project. *Faraday Discuss.* doi:10.1039/d0fd00097c

Han, Y., Chen, W., Chatzidiakou, L., Krause, A., Yan, L., Zhang, H., . . . Zhu, T. (2020). Effects of AIR pollution on cardiopulmonary disease in urban and peri-urban residents in Beijing: protocol for the AIRLESS study. *Atmospheric Chemistry and Physics*, 20(24), 15775-15792. doi:10.5194/acp-20-15775-2020

He, L., Cui, X., Xia, Q., Li, F., Mo, J., Gong, J., . . . Zhang, J. J. (2020). Effects of personal air pollutant exposure on oxidative stress: Potential confounding by natural variation in melatonin levels. *Int J Hyg Environ Health*, 223(1), 116-123. doi:10.1016/j.ijheh.2019.09.012

He, L., Lin, Y., Wang, X., Liu, X. L., Wang, Y., Qin, J., . . . Zhang, J. J. (2020). Associations of ozone exposure with urinary metabolites of arachidonic acid. *Environ Int*, 145, 106154. doi:10.1016/j.envint.2020.106154

James, P., Banay, R. F., Hart, J. E., & Laden, F. (2015). A Review of the Health Benefits of Greenness. *Curr Epidemiol Rep*, 2(2), 131-142. doi:10.1007/s40471-015-0043-7

Ji, J. S., Zhu, A., Bai, C., Wu, C.-D., Yan, L., Tang, S., . . . James, P. (2019). Residential greenness and mortality in oldest-old women and men in China: a longitudinal cohort study. *The Lancet Planetary Health*, 3(1), e17-e25. doi:10.1016/s2542-5196(18)30264-x

Kioumourtzoglou, M. A., Schwartz, J., James, P., Dominici, F., & Zanobetti, A. (2016). PM_{2.5} and Mortality in 207 US Cities: Modification by Temperature and City Characteristics. *Epidemiology*, 27(2), 221-227. doi:10.1097/ede.0000000000000422

- Li, W., Wilker, E. H., Dorans, K. S., Rice, M. B., Schwartz, J., Coull, B. A., . . . Mittleman, M. A. (2016). Short-Term Exposure to Air Pollution and Biomarkers of Oxidative Stress: The Framingham Heart Study. *J Am Heart Assoc*, 5(5). doi:10.1161/jaha.115.002742
- Li, Z., Liu, Q., Xu, Z., Guo, X., & Wu, S. (2020). Association between short-term exposure to ambient particulate air pollution and biomarkers of oxidative stress: A meta-analysis. *Environ Res*, 191, 110105. doi:10.1016/j.envres.2020.110105
- Liang, L., Cai, Y., Barratt, B., Lyu, B., Chan, Q., Hansell, A. L., . . . Tong, Z. (2019). Associations between daily air quality and hospitalisations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013-17: an ecological analysis. *Lancet Planet Health*, 3(6), e270-e279. doi:10.1016/s2542-5196(19)30085-3
- Liu, L., Urch, B., Szyszkowicz, M., Evans, G., Speck, M., Van Huang, A., . . . Silverman, F. S. (2018). Metals and oxidative potential in urban particulate matter influence systemic inflammatory and neural biomarkers: A controlled exposure study. *Environ Int*, 121(Pt 2), 1331-1340. doi:10.1016/j.envint.2018.10.055
- Miller, M. R. (2014). The role of oxidative stress in the cardiovascular actions of particulate air pollution. *Biochem Soc Trans*, 42(4), 1006-1011. doi:10.1042/bst20140090
- Miller, M. R., Shaw, C. A., & Langrish, J. P. (2012). From particles to patients: oxidative stress and the cardiovascular effects of air pollution. *Future Cardiol*, 8(4), 577-602. doi:10.2217/fca.12.43
- NASA. Moderate Resolution Imaging Spectroradiometer. Retrieved from <https://modis.gsfc.nasa.gov>
- Nunes, R. A., Branco, P. T., Alvim-Ferraz, M. C., Martins, F. G., & Sousa, S. I. (2015). Particulate matter in rural and urban nursery schools in Portugal. *Environ Pollut*, 202, 7-16. doi:10.1016/j.envpol.2015.03.009

- O'Callaghan-Gordo, C., Kogevinas, M., Cirach, M., Castaño-Vinyals, G., Aragonés, N., Delfrade, J., . . . Nieuwenhuijsen, M. J. (2018). Residential proximity to green spaces and breast cancer risk: The multicase-control study in Spain (MCC-Spain). *Int J Hyg Environ Health*, 221(8), 1097-1106. doi:10.1016/j.ijheh.2018.07.014
- Pan, L., Yao, E., & Yang, Y. (2016). Impact analysis of traffic-related air pollution based on real-time traffic and basic meteorological information. *J Environ Manage*, 183(Pt 3), 510-520. doi:10.1016/j.jenvman.2016.09.010
- Peng, W., Jiang, M., Shi, H., Li, X., Liu, T., Li, M., . . . Wang, Y. (2020). Cross-sectional association of residential greenness exposure with activities of daily living disability among urban elderly in Shanghai. *Int J Hyg Environ Health*, 230, 113620. doi:10.1016/j.ijheh.2020.113620
- Ren, C., Fang, S., Wright, R. O., Suh, H., & Schwartz, J. (2011). Urinary 8-hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage induced by ambient pollution in the Normative Aging Study. *Occup Environ Med*, 68(8), 562-569. doi:10.1136/oem.2010.056358
- Rodríguez-San Nicolás, A., SÁnchez-Rodríguez, M. A., Zacarías-Flores, M., Correa-Muñoz, E., & Mendoza-Núñez, V. M. (2020). [Relationship between central obesity and oxidative stress in premenopausal versus postmenopausal women]. *Nutr Hosp*, 37(2), 267-274. doi:10.20960/nh.02552
- Saenen, N. D., Martens, D. S., Neven, K. Y., Alfano, R., Bové, H., Janssen, B. G., . . . Nawrot, T. S. (2019). Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? *Clin Epigenetics*, 11(1), 124. doi:10.1186/s13148-019-0688-z
- Sajous, L., Botta, A., & Sari-Minodier, I. (2008). [Urinary 8-hydroxy-2'-deoxyguanosine: a biomarker of environmental oxidative stress?]. *Ann Biol Clin (Paris)*, 66(1), 19-29. doi:10.1684/abc.2008.0188
- Seydanur Dengizek, E., Serkan, D., Abubekir, E., Aysun Bay, K., Onder, O., & Arife, C. (2019). Evaluating clinical and laboratory effects of ozone in non-surgical

periodontal treatment: a randomized controlled trial. *J Appl Oral Sci*, 27, e20180108. doi:10.1590/1678-7757-2018-0108

Shah, A. S., Lee, K. K., McAllister, D. A., Hunter, A., Nair, H., Whiteley, W., . . . Mills, N. L. (2015). Short term exposure to air pollution and stroke: systematic review and meta-analysis. *Bmj*, 350, h1295. doi:10.1136/bmj.h1295

Stieb, D. M., Shutt, R., Kauri, L. M., Roth, G., Szyszkowicz, M., Dobbin, N. A., . . . Dales, R. E. (2018). Cardiorespiratory Effects of Air Pollution in a Panel Study of Winter Outdoor Physical Activity in Older Adults. *J Occup Environ Med*, 60(8), 673-682. doi:10.1097/jom.0000000000001334

Twohig-Bennett, C., & Jones, A. (2018). The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes. *Environ Res*, 166, 628-637. doi:10.1016/j.envres.2018.06.030

Valavanidis, A., Vlachogianni, T., & Fiotakis, C. (2009). 8-hydroxy-2'-deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, 27(2), 120-139. doi:10.1080/10590500902885684

Wang, C., Bi, J., & Olde Rikkert, M. G. M. (2018). Early warning signals for critical transitions in cardiopulmonary health, related to air pollution in an urban Chinese population. *Environ Int*, 121(Pt 1), 240-249. doi:10.1016/j.envint.2018.09.007

Wang, C., Xu, J., Yang, L., Xu, Y., Zhang, X., Bai, C., . . . He, J. (2018). Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet*, 391(10131), 1706-1717. doi:10.1016/s0140-6736(18)30841-9

Weissmann, N. (2018). Chronic Obstructive Pulmonary Disease and Pulmonary Vascular Disease. A Comorbidity? *Ann Am Thorac Soc*, 15(Suppl 4), S278-s281. doi:10.1513/AnnalsATS.201808-532MG

World Population Policies 2019. (2019). *Department of Economic and Social Affairs, Population Division (2019)*. Retrieved from www.un.org/development/desa/pd/themes/population-policies.

Yeager, R., Riggs, D. W., DeJarnett, N., Tollerud, D. J., Wilson, J., Conklin, D. J., . . . Bhatnagar, A. (2018). Association Between Residential Greenness and Cardiovascular Disease Risk. *J Am Heart Assoc*, 7(24), e009117. doi:10.1161/JAHA.118.009117

Zhang, G., Jiang, F., Chen, Q., Yang, H., Zhou, N., Sun, L., . . . Ao, L. (2020). Associations of ambient air pollutant exposure with seminal plasma MDA, sperm mtDNA copy number, and mtDNA integrity. *Environ Int*, 136, 105483. doi:10.1016/j.envint.2020.105483

Zhang, H., Wang, Q., He, S., Wu, K., Ren, M., Dong, H., . . . Huang, C. (2020). Ambient air pollution and gestational diabetes mellitus: A review of evidence from biological mechanisms to population epidemiology. *Sci Total Environ*, 719, 137349. doi:10.1016/j.scitotenv.2020.137349

Zhao, P., Li, S., & Liu, D. (2020). Unequable spatial accessibility to hospitals in developing megacities: New evidence from Beijing. *Health Place*, 65, 102406. doi:10.1016/j.healthplace.2020.102406